

I. **REMARKS**

The final Office Action dated June 6, 2008, has been received and carefully noted. The following remarks are submitted as a full and complete response thereto.

Claims 7-12 are pending. Claims 7-10 were withdrawn from consideration by the Examiner.

No amendments to the claims or specification are made by this response.

Rejections under 35 U.S.C. § 103

1. *Yang et al.*

Claim 11 has been rejected under 35 U.S.C. § 103(a) over Yang et al. (U.S. Patent No. 4,740,376). Applicants traverse the rejection.

Claim 11 is directed to a "method of producing solid pharmaceutical preparations, comprising using the polyvinylacetates of claim 10 as a binder, alone or in combination with other binders, in base granulates or granulates that contain an active substance, wherein the polyvinylacetates are used in a solution with solvent or as a solid powder." Applicants submit that the polyvinylacetates of claim 10 have the following claimed properties: mean molecular weight between 10,000 and 40,000 Daltons, remnant monomer content of less than 2 ppm by weight, water content less than 1.5% by weight, total acidity referred to acetic acid less than 0.5% by weight, peroxide content of 0.0%, and glass transition temperature of 35°C to 39°C.

Before commenting on the present rejection, Applicants submit the following comments. Applicants submit that commercially solid polyvinylacetate (PVAc) (not the emulsion or suspension forms) which can be normally purchased as industrial products

typically have an upper limit of vinyl acetate content of 200 ppm, which is 100 times higher than the claimed amount of PVAc (2 ppm). Applicants submit that the claimed PVAc in pharmaceutical formulations present advantages, due to its higher purity, which allows for the minimization of undesirable interactions between impurities and different active principles and excipients.

Applicants further submit that PVAc is not soluble in water. Therefore, Applicants submit that one of ordinary skill in the art would therefore not consider water as a possible solvent in PVAc solutions and would rather consider organic polar volatile solvents for such solutions, which is usually used for wet granulation in the pharmaceutical industry. Applicants submit that water is typically only present in emulsions or suspensions of PVAc which are necessarily obtained by means of emulsion or suspension polymerization of vinyl acetate, a process that normally produces PVAc of much higher molecular mass (as chain transfer is very low), as is the PVAc described in this application. Applicants submit that PVAc in emulsions or suspensions usually contain more impurities (such as surfactants and thickeners) beside relatively higher contents of vinyl acetate, compared to polymer obtained in solution, and the micelles of PVAc are saturated with water. Applicants submit that the use in wet granulation of emulsions is limited also by the fact that higher temperatures are required for the drying of the granulates, which is not always possible with many active principles that can decompose.

Applicants submit that while PVAc is not soluble in water, water is soluble in

PVAc. Applicants submit that PVAc is an amorphous polymer, and a PVAc with a homogeneous water content above the glass transition temperature ( $T_g$ ) has to be regarded as a quasi solid solution. Applicants submit that having a water content below the  $T_g$  should be regarded as a frozen solution. Due to thermodynamic reasons, Applicants submit that PVAc can take only a certain quantity of water. For example, at 37°C, Applicants submit that this quantity is about 3.7% of the total weight of the solid solution. Applicants submit that this is discussed in the present specification (see Figures 4 and 5). Applicants submit that higher water contents can be obtained, because phase separation occurs and the formed water droplets are occluded within the polymer (see Fig. 4).

Applicants submit that it is well known that the vapor pressure of a liquid that is present in a binary solution with a non-volatile compound (which may be a solid) is decreased compared to the vapor pressure of the mentioned liquid in pure form. Applicants submit that this is a special case of the law of Raoult. Applicants submit that this means that, for example, in the case of water dissolved in PVAc, higher temperatures than the boiling point of pure water are needed in order for the liquid to "boil." Applicants submit that the same concept applies for vinyl acetate. Therefore, Applicants submit that the "melting" of wet PVAc at 100°C or even above would not mean that water evaporates. But, Applicants submit, even if the temperature is high enough or concomitantly the external pressure is reduced, water or vinyl acetate would be released very slowly from the polymer, due to the high viscosity of the system. Applicants submit that the viscosity increases very fast for lower contents of water, as

discussed in the specification (see Figure 1). Applicants submit that Figure 1 shows that “molten” PVAc samples of with same structure and molecular mass may have different properties, in this case, the viscosity.

Further, Applicants submit that the term “molten” is not quite proper for a system having PVAc and water, since amorphous systems do not have a melting temperature. But, Applicants submit, if such “molten” polymers as shown in Figure 1 are cooled to room temperature, they will show very different values for the glass transition temperature, due to their different water contents. For example, Applicants submit that pure, dry PVAc has a Tg of 39°C and PVAc with 3.5% of water has a Tg below 20°C. Applicants submit that this means again that different samples of PVAc, with the same structure, which were “molten” and thereafter cooled, may have different properties, not only the properties of Tg and viscosity, but also the properties of water and vinyl acetate content. Applicants submit that a PVAc with a Tg below 20°C can hardly be milled at room temperature, and even at lower temperatures, since the milling process would increase the temperature above the Tg, which would imply that the polymer becomes plastic. Applicants submit that the capability of being milled is another property that can be different by polymer samples of same molecular mass that were former “molten”.

Applicants submit that Yang et al. does not teach or suggest the presently claimed invention. Applicants respectfully submit that although Yang et al. discloses pharmaceutical compositions that are produced in a melt, the Examiner improperly assumes that any water or vinyl acetate monomer present is evaporated and that the

water content of the polymer would obviously less than 1.5%.

For at least the reasons stated above, Applicants submit that Yang et al. does not teach or suggest the presently claimed invention and respectfully request reconsideration and withdrawal of the rejection of claim 11 under 35 U.S.C. § 103(a) over Yang et al.

2. Sa

Claim 11 was rejected under 35 U.S.C. § 103(a) over Sa (Drug Development and Industrial Pharmacy, 17(6), 893-900 (1991)). Applicants traverse the rejection.

Claim 11 and the features of the presently claimed invention have been discussed above.

Applicants submit that Sa does not teach or suggest the presently claimed invention. For example, Applicants submit that the Examiner improperly assumes that the polyvinylacetate described in Sa has a low water content since the microspheres of Sa, which contain theophylline and polyvinylacetate, were dried in a vacuum desiccator. Applicants submit that the described procedure is not an industrial one and is not suited for purifying a polymer whose use is not restricted to the production of microspheres. Applicants submit that the high purity of the presently claimed polyvinylacetates cannot be achieved according to the method disclosed in Sa.

Applicants further submit that the polymer described in the present application presents higher purity compared to other polymers that are commercially available. Applicants submit that the polymer described in this application have pharmaceutical

use not restricted to formulations in which the polymer has to be melted. Applicants submit that most active principles would not resist such a procedure and only a few very stable actives, like theophylline, could be employed.

Further, Applicants submit that microencapsulation is one of the existing processes for the obtaining of pharmaceutical solid forms. Applicants submit that microspheres can be obtained in different ways, depending on the polymers used and on the properties of the active principle. Applicants submit that Sa describes a method for the obtaining of microspheres that contain theophylline and PVAc in comparable amounts. Applicants submit that in Sa, theophylline crystals were suspended in an acetone PVAc solution and with span 80 and vigorously stirred at 15°C, and an emulsion in heavy liquid paraffin was obtained. Applicants submit that stirring was continued for a sufficient period (although the exact time period was not disclosed) to evaporate off acetone at room temperature. Applicants submit that the microspheres were made rigid by adding hexane, dropwise, and then collected by filtration, washed with cold hexane and kept in a vacuum desiccator in a cool place. Applicants submit that this is not an industrial procedure. Applicants submit that the evaporation of acetone at 15°C occurs over a long period of time, which could be made faster by the blowing of air. Applicants submit that all polar compounds present (water and vinyl acetate) would be retained mostly in the polymer rich solution droplets, due to affinity to the polymer. Applicants submit that higher temperatures (which theophylline and PVAc would resist) are not used, likely because the polymer-rich droplets could stick together. Applicants submit that washing with hexane would not extract water or completely

extract vinyl acetate residual monomer (both presenting higher affinity to the polymer as to the solvent). Applicants submit that in Sa, the microspheres were dried under vacuum in a desiccator at a cool temperature, a procedure that may last a prolonged period of time. Any water and vinyl acetate impurities would be retained under those mild temperature conditions for the reasons already discussed (low vapor pressure, diffusion through a very viscous medium). Applicants submit that the described drying in the desiccator of the microspheres was possible due to the fact that small amounts were produced. Otherwise, Applicants submit that the weight of the microspheres from the upper layers would cause the microspheres of the lower layers to agglomerate before complete drying. Applicants submit that when water remains within the polymer, the risk of agglomeration of the microspheres at room temperatures is high (due to the considerable lowering of the Tg that small quantities of water may cause).

Applicants submit that for the discussed reasons, even in the special case of microencapsulation, it is desirable that the employed PVAc is as free as possible of contaminants, specially vinyl acetate and water. Therefore, Applicants submit that the claimed polymer has considerable advantages.

For at least the reasons stated above, Applicants submit that Sa does not teach or suggest the presently claimed invention and respectfully request reconsideration and withdrawal of the rejection of claim 11 over Sa.

3. *Yang et al., in view of Sa*

Claims 11-12 were rejected under 35 U.S.C. § 103(a) over Yang et al., in view of Sa. Applicants traverse the rejection.

As discussed above, Applicants submit that the presently claimed invention is not taught by Yang et al. and Sa. Applicants submit that the deficiencies of Yang et al. are not cured by Sa, and neither reference teaches the polyvinylacetates of the presently claimed invention.

Therefore, Applicants respectfully request reconsideration and withdrawal of the rejection of claims 11-12 under 35 U.S.C. § 103(a) over Yang et al., in view of Sa.

## II. CONCLUSION

Applicants respectfully submit that this application is in condition for allowance and such action is earnestly solicited. If the Examiner believes that anything further is desirable in order to place this application in even better condition for allowance, the Examiner is invited to contact Applicants' undersigned representative at the telephone number listed below to schedule a personal or telephone interview to discuss any remaining issues.

In the event this response is not timely filed, the Applicants hereby petition for an appropriate extension of time. The fee for this extension, along with any other additional fees which may be required with respect to this response, may be charged to Deposit Account No. 01-2300, referencing Attorney Docket No. 024273-00001.

Respectfully submitted,



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